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Case report

Adult-onset asthma and periocular xanthogranulomas associated with systemic IgG4-related disease

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ABSTRACT

Purpose: The aim of this study was to report a case of Adult-Onset Asthma with Periocular Xanthogranulomas (AAPOX) associated with systemic IgG4-related disease (IgG4-RD).**Observations:** A 57-year-old man presented with bilateral periorbital swelling for 1 year. Histopathology of a left orbital biopsy showed fibro vascular connective tissue inundated with foamy, lipid-laden histiocytes and Touton giant cells with lymphocytic inflammation. Additional stains revealed CD68 positivity, and S100 negativity. The IgG and IgG4 stained slides showed increased IgG4 positive plasma cells but did not meet the criteria for IgG4-related orbital disease. His IgG4 serology was elevated, and IgG4 staining of his tissue previously diagnosed as autoimmune sclerosing pancreatitis was found to meet the criteria for IgG4-RD.**Conclusion and importance:** AAPOX can be associated with systemic IgG4-RD.© 2016 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Adult-Onset Asthma with Periocular Xanthogranulomas (AAPOX) is a systemic disorder characterized by adult-onset asthma, lymphadenopathy, and periocular xanthogranulomatous disease. IgG4-related disease (IgG4-RD) is an immune mediated fibrosing inflammatory condition that can affect almost any organ. We present a patient with adult-onset asthma, biopsy proven periocular xanthogranulomas, and systemic IgG4-RD.

2. Case report

A 57-year-old male presented to the oculoplastics service with bilateral periorbital swelling that progressed over one year (Fig. 1). The patient provided written consent for publication of personal information including medical record details and photographs. The swelling temporarily regressed with courses of oral steroids, but always recurred after treatment was discontinued. His past medical

history was extensive and included biopsy proven chronic sialadenitis (2001); lymphoplasmacytic sclerosing pancreatitis for which he underwent a Whipple procedure (2002), ureteral stenting of a ureteral scar causing left-sided hydronephrosis (2002), adult-onset asthma (2002), hypersplenism, clinical xanthelasma of the left upper eyelid (2003), hypo cellular bone marrow with panhypoplasia (2003), and recent migratory arthritis and intermittent swelling/redness of joints. Family history was significant for Rosai-Dorfman disease and adult-onset-asthma (identical twin brother), and chronic thrombocytopenia (mother and daughter).

A left anterior orbitotomy and orbital biopsy was performed (2015). Histopathology revealed fibro vascular connective tissue with striated muscle and deep empty lipid spaces inundated with foamy, lipid-laden S100- and CD68⁺ (not shown) histiocytes and Touton-type giant cells (Fig. 2). There were well-formed lymphoid follicles with germinal centers surrounded by mature lymphocytes. Acid Fast stain did not show any microorganisms.

Due to concern for Erdheim-Chester Disease (ECD), a whole body Positron emission tomography (PET) and computerized tomography (CT) study were requested to assess for long bone lesions and organ involvement, and BRAF V600E mutation analysis was ordered. There was bilateral moderate-to-intense symmetrical ¹⁸F-Fludeoxyglucose (¹⁸F-FDG) uptake in the periorbital areas, along

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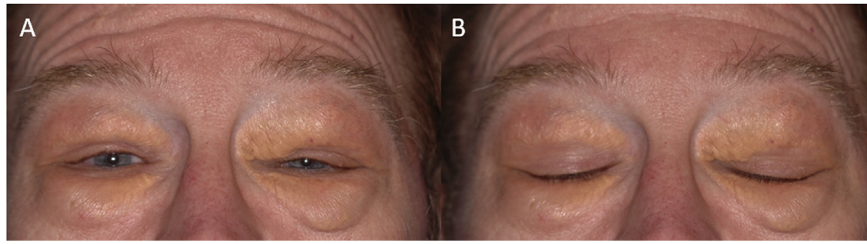


Fig. 1. A&B. Frontal view of yellow periorbital swelling. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

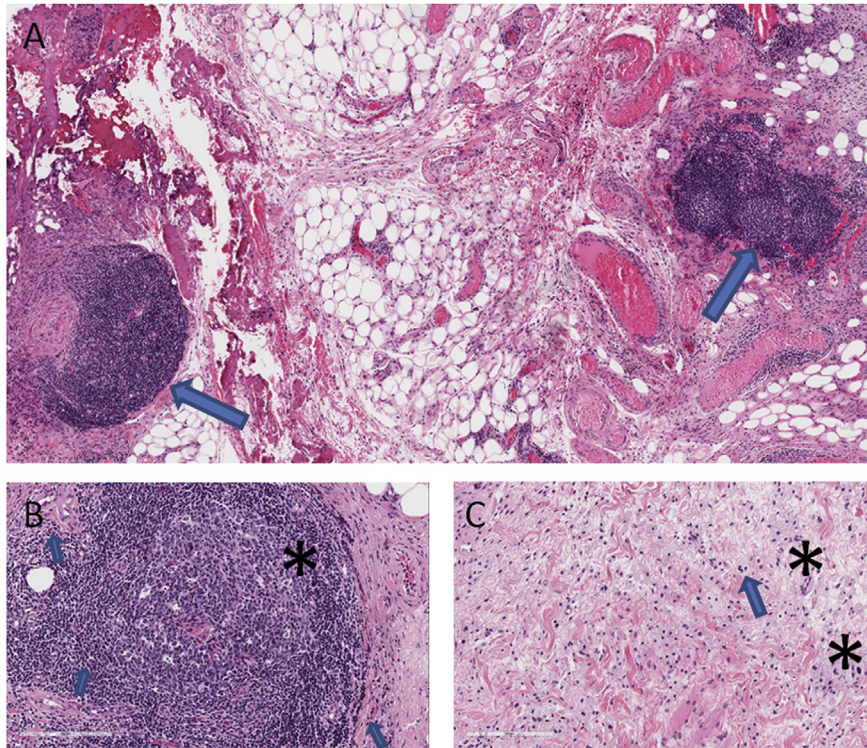


Fig. 2. Hematoxylin-eosin-stained sections. **A.** Low-power view showing infiltration by foamy histiocytes and mature lymphoid follicles (Arrows, original magnification $\times 4$). **B.** Higher-power view focusing on a prominent lymphoid follicle (Star) and scattered eosinophils (Small arrows, original magnification $\times 19$). **C.** Foamy macrophages (Stars) and multinucleated giant cells (Arrow) infiltrating orbicularis oculi muscle (original magnification $\times 19$).

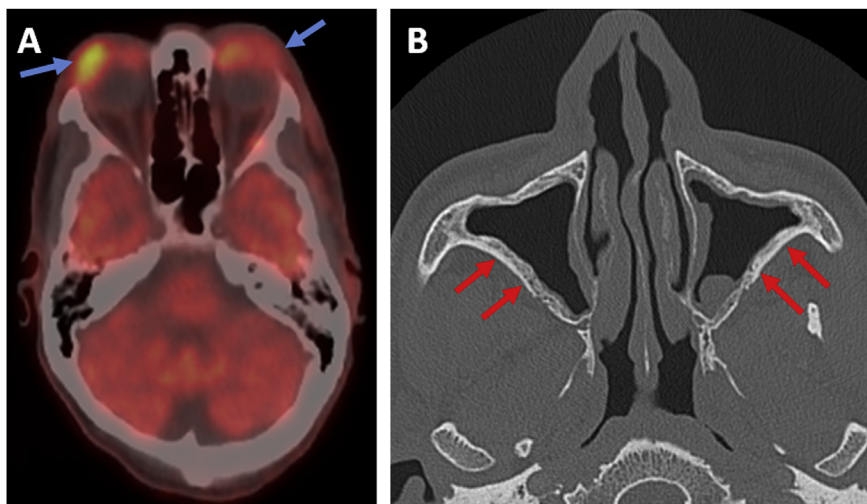


Fig. 3. **A.** ^{18}F -FDG avid anterior orbits (Arrows, ^{18}F -Fludeoxyglucose (^{18}F -FDG) Positron Emission Tomography (PET)/Computed Tomography (CT)). **B.** Sclerosis and expansion of the maxillary bones (Arrows, CT).

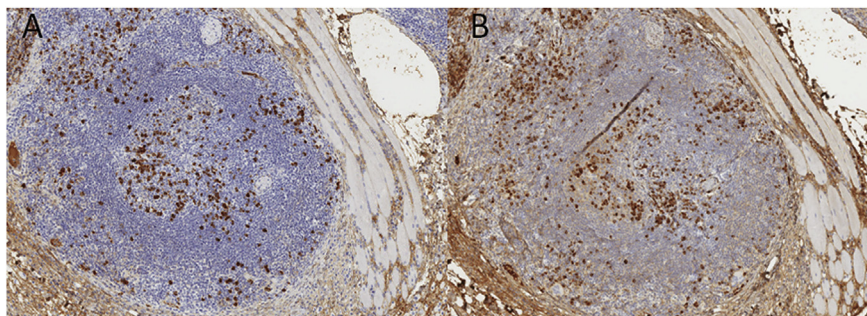


Fig. 4. Immunohistochemical stains of left anterior orbital tissue show areas of increased absolute and relative numbers of IgG4 expressing plasma cells (**A**, IgG4, $\times 5$, **B**, IgG, $\times 5$).

Table 1

Cases of adult-onset asthma with periocular xanthogranulomas with IgG4-Related disease.

	Age at onset/ diagnosis (years)	Gender	Ophthalmic presentation	Systemic presentation	Treatment
Current Case	44/57	M	Bilateral yellow upper and lower eyelid swelling	Adult-onset-asthma, lymphoplasmacytic sclerosing pancreatitis	Methylprednisolone 100mg IV before rituximab 1000mg x 2
London et al. (2015) [17]	55/65	M	Bilateral yellow upper and lower eyelid swelling	Adult-onset-asthma, allergic sinusitis, cervical lymphadenopathy, left cheek swelling	Prednisone 1mg/kg/day tapered to 5mg/ day
London et al. (2015)	48/52	M	Bilateral orange upper and lower eyelid swelling	Adult-onset-asthma, obstructive sleep apnea, allergic sinusitis, right inguinal adenopathy	Prednisone 1mg/kg/day tapered to 5mg/ day and transitioned to low dose methotrexate
London et al. (2015)	24/33	F	Yellow swelling of the left upper eyelid	Adult-onset-asthma, allergic sinusitis, bilateral axillary adenopathy	Prednisone 1mg/kg/day tapered to 10mg/ day and transitioned to low dose methotrexate
Roggin et al. (2007) [18]	58/61	M	Bilateral yellow upper and lower eyelid swelling	Adult-onset-asthma, nasal polyps, cutaneous hypersensitivity, lymphoplasmacytic sclerosing pancreatitis, cervical lymphadenopathy	Prednisone 5mg/day

with diffuse mild-moderate inflammatory mucosal thickening, sclerosis, and expansion of the bilateral maxillary sinus walls, consistent with chronic sinusitis (Fig. 3). Other areas of signal uptake included the left psoas and iliacus muscles, and the prostate gland. The absence of long bone involvement or BRAF V600E mutation made ECD unlikely.

After the negative workup for ECD, IgG4 serology and IgG4/IgG staining were ordered to rule out IgG4-RD. Though there were many IgG4 positive cells, the characteristic findings of IgG4-related orbital disease described by Umehara and Deshpande et al., such as IgG4+/IgG + cell ratio $>40\%$, >100 IgG4+ plasma cells/high power field, storiform fibrosis, and obliterative phlebitis were not present (Fig. 4) [1,2]. IgG4 serology however was highly elevated at 236 mg/dL (range 7–89), and his slides previously diagnosed as autoimmune sclerosing pancreatitis were re-reviewed, assisted by IgG4 staining and found to meet the criteria for systemic IgG4-RD. He was treated with 100mg methylprednisolone IV before rituximab 1000mg infusion x 2 doses per the trial by Carruthers et al. for treating IgG4-RD, with mild improvement of his periocular swelling over the past 6 months [3].

3. Discussion

Orbital xanthogranulomatous disease in adults is a rare, non-Langerhans (type II) histiocytosis, categorized into four syndromes: adult onset xanthogranuloma (AOX), AAPOX, ECD, and necrobiotic xanthogranuloma (NBX). This patient was initially diagnosed with xanthelasma several years prior, and like

xanthelasma, they may all present clinically as yellow periocular masses, and are difficult to distinguish based off of histology alone.

Xanthelasma features foamy histiocytes, but is limited to the superficial dermis. AOX is characterized by xanthogranulomatous inflammation localized to the anterior orbit, without systemic findings [4].

AAPOX was first described by Jakobiec et al., in 1993 in a series of patients with eyelid and orbital lesions with histopathologic features appearing similar to those seen in ECD [5]. Patients with AAPOX lack the typical systemic associations of ECD, but have the onset of differing degrees of adult-onset asthma near the time that their periocular lesions appear. Our patient's asthma symptoms began within one year of his periocular process. The lymphoid follicles with germinal centers and capillary endothelial proliferation within lymphoid infiltrates on histology help distinguish them from the other processes.

ECD often has more posterior orbital and intraconal involvement than the other syndromes, is the most deadly, and is strongly associated with the oncogenic BRAF V600E mutation [6]. Sclerosis of the long bones is seen in up to 96% of cases, but clinical manifestations may include diabetes insipidus, neurological, constitutional, retroperitoneal, cutaneous, cardiovascular, respiratory, and other symptoms [7,8].

NBX presents as red-orange papules involving the periorbital region 80% of the time. Local involvement may cause scleritis, keratitis, proptosis, scarring, and ulceration, but multi-organ involvement has been documented. Hematologic abnormalities such as monoclonal gammopathy, multiple myeloma, Hodgkin and non-Hodgkin lymphoma, chronic lymphocytic leukemia, and

myelodysplastic syndrome are often associated and can manifest as long as 20 years after the skin lesions [9].

With time, the links between orbital xanthogranulomatous disease and systemic IgG4-RD are being elucidated [10–12]. IgG4-RD is a systemic inflammatory fibrosing disorder, which may involve almost every organ. Ophthalmic manifestations include: dacryoadenitis, orbital pseudotumor, eosinophilic angiocentric fibrosis, orbital myositis, scleritis, and nasolacrimal duct obstruction. Systemic manifestations include Riedel's thyroiditis, idiopathic hypertrophic pachymeningitis, pericardial involvement, pulmonary pseudotumor/fibrosis, autoimmune pancreatitis type 1, sclerosing cholangitis, tubulointerstitial nephritis, membranous nephropathy, pseudotumors of the kidney, retroperitoneal fibrosis, aortitis, lymphadenopathy, and others [13]. Due to the nature of the disease, many specialty teams were involved in our patient's care before his autoimmune pancreatitis, ureteral stenosis, sialadenitis, chronic sinusitis, etc. were linked to the same systemic process.

His identical twin brother carries a diagnosis of Rosai-Dorfman disease, a histiocytic disorder characterized by S100 + and CD68 + histiocytes with intact lymphocytes within their cytoplasm (emperipolesis). Interestingly Rosai-Dorfman disease has also shown overlap with IgG4-RD [14–16].

Including this case, there have been 5 definitive cases of AAPOX associated with systemic IgG4-RD (Table 1). All patients required long-term treatment with low dose steroids, or steroid sparing agents such as methotrexate or rituximab. Review of the literature for orbital xanthogranulomatous inflammation in adults reveals many cases suspicious for AAPOX and IgG4-RD, and we believe that the association is more common than the paucity of published cases suggests.

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